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Comparative effectiveness of dabigatran, rivaroxaban, apixaban and warfarin in the management of patients with non-valvular atrial fibrillation

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Abstract

Alternative anticoagulants to warfarin (dabigatran, rivaroxaban and apixaban) are becoming available for the prevention of thromboembolic stroke in atrial fibrillation, but there is a lack of information on their comparative effectiveness. We evaluated this using a discrete event simulation with a lifetime horizon of analysis, based on an indirect comparison of the RE-LY, ROCKET-AF and ARISTOTLE trial results for patients with the characteristics of the US atrial fibrillation population. Over a lifetime, apixaban, dabigatran and rivaroxaban accrued 0.130 (95% central range [CR] −0.030 to 0.264), 0.106 (95% CR −0.048 to 0.248) and 0.095 (95% CR −0.052 to 0.242) more quality-adjusted life-years than warfarin, respectively, with apixaban having a 55% probability of accruing the highest total lifetime QALYs. In the absence of a definitive trial, and acknowledging the limitations of an indirect comparison, the available evidence suggests apixaban to be the more effective anticoagulant.

Keywords

Anticoagulants; atrial fibrillation; meta-analysis; comparative effectiveness; stroke

Introduction

Atrial fibrillation (AF) is estimated to affect 2.5 million people in the United States, and results in a fivefold increase in the risk of ischemic stroke[1,2]. Associated costs exceed $7 billion annually[3]. Antithrombotic agents have proven benefits in preventing stroke in patients with AF. Until recently, vitamin K antagonists, such as warfarin, were the only form of oral thromboprophylactic anticoagulation treatment[4]. Although clinically effective and inexpensive, warfarin increases the risk of hemorrhage, interacts with many drugs and, because of the considerable variability in patient response, requires careful monitoring[5,6].

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Newer oral anticoagulants, which include the direct thrombin inhibitor dabigatran etexilate (hereafter referred to as dabigatran), and the direct factor Xa inhibitors rivaroxaban and apixaban, have recently been developed. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study evaluated two doses (110mg and 150mg twice daily) of dabigatran as an alternative to warfarin in 18,113 patients with at least one risk factor for stroke[7]. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared rivaroxaban with warfarin in 14,264 patients at elevated risk of stroke[8]. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared apixaban with warfarin in 18,201 patients with at least one risk factor for stroke[9].

After median follow up periods of approximately two years, the primary outcome of stroke or systemic embolism showed a potential improvement in the intention-to-treat population with all three alternatives, demonstrating superiority of the licensed 150mg dose of dabigatran (1.11% v 1.71% per year; $p<0.001$) and apixaban (1.27% v 1.60% per year; $p=0.01$) and non-inferiority of rivaroxaban (2.1% v 2.4% per year; $p=0.12$), compared with warfarin. Rates of major bleeding were not significantly different between dabigatran 150mg and warfarin or between rivaroxaban and warfarin, but apixaban was associated with a lower risk of major bleeding (2.13% v 3.09% per year; $p<0.001$).

Dabigatran, rivaroxaban and apixaban have all been approved by the US Food and Drug Administration but whilst their efficacies in relation to warfarin have been demonstrated, their comparative effectiveness remains unknown. With no prospect of a head-to-head trial, we describe an adjusted, indirect comparison to help guide treatment selection. The analysis assesses the trade-offs in thrombotic and bleeding risks for all four anticoagulants, and incorporates a preference-based, patient-centred outcome, the quality-adjusted life-year (QALY), to combine health-related quality of life with survival. Our analysis acknowledges differences in trial designs and populations, and their potential impacts on estimated comparative effectiveness, by adopting a probabilistic approach for a range of plausible scenario analyses.

Results

The results of the simulations at 2 years matched the results of each trial. No value deviated by more than 3.2% (data not presented), a level of variability that would be expected given the stochastic nature of the simulation. At 2 years, apixaban accrued 0.15 more quality-adjusted life-weeks than dabigatran, 0.26 more than rivaroxaban, and 0.78 more than warfarin.

Clinical outcomes and net health benefit

In the base-case analysis, apixaban, dabigatran and rivaroxaban extended life by 2.05, 1.51 and 1.10 months respectively, compared with warfarin (table 1). The corresponding incremental net health benefits were 0.130 (95% central range [CR] −0.030 to 0.264), 0.106 (95% CR −0.048 to 0.248) and 0.095 (95% CR −0.052 to 0.242) QALYs. In pairwise comparisons, using warfarin as the comparator, apixaban, dabigatran and rivaroxaban were associated with a positive incremental net health benefit in 90%, 84% and 82% of simulations, respectively. Using rivaroxaban as a comparator, apixaban and dabigatran were associated with an incremental net health benefit in 71% and 61% of simulations, and finally apixaban was associated with an incremental net health benefit against dabigatran in 65% of simulations.

Lifetime incidences of stroke or systemic embolism were 33.6% lower with apixaban, 17.0% lower with dabigatran and 6.7% lower with rivaroxaban, when compared to warfarin. Lifetime incidences of major hemorrhagic events were 21.3% lower with apixaban, but 7.0% and 1.3% higher with rivaroxaban and dabigatran, respectively. Incidences of myocardial infarction were 10.7% lower with rivaroxaban and 6.5% lower with apixaban, but 22.3% higher with dabigatran.

The relative effects of each treatment on the two constructs of the QALY, health-related quality of life and life-years gained, is illustrated in efigure 1.

Univariate parameter sensitivity analysis results are presented in the form of tornado plots (figure 1).

Structural sensitivity analysis

In the probabilistic sensitivity analysis of structural uncertainty, the base-case ordering of QALYs (apixaban, dabigatran, rivaroxaban, warfarin, in descending order) was replicated in 65.1% of the simulations. The alternative ordering (dabigatran, apixaban, rivaroxaban, warfarin) occurred in 17.2% of simulations, and the ordering (apixaban, rivaroxaban, dabigatran, warfarin) occurred in 13.4% of simulations. No other ordering occurred in more than 1% of simulations. Overall, apixaban accrued the highest number of QALYs in 79.9% of the simulations, dabigatran in 18.0% and rivaroxaban in 2.1%, with warfarin never accruing the highest number.

Using a Markov model, instead of a discrete event simulation, led to changes in both event rates and the numbers of QALYs and life-years accrued. However, the same ordering was maintained, with apixaban the most effective with 8.49 QALYs, then dabigatran with 8.35, rivaroxaban with 8.28 and warfarin with 8.08 QALYs.

Subgroup analyses

Among the subgroups analysed, the ordering of medicines according to mean QALYs and probability of being most effective was consistent with the base-case analysis (table 2, figure 2). Apixaban had the highest probability of being the most effective in patients with impaired renal function, and the lowest in older populations (≥75 years), but these probabilities were over a very narrow range (50.1% to 61.6%).

Discussion

Based on an accepted method of comparative effectiveness research (CER) that preserves the randomisation of treatment allocation, and which results in an adjusted, indirect comparison[15], apixaban appears as the most effective oral anticoagulant, followed by dabigatran, rivaroxaban then warfarin. Differences were driven principally by differential stroke rates and the risks of intracranial hemorrhage, which were lower for all newer agents compared with warfarin. This ordering remained consistent across patient subgroups, though the differences in net health benefits changed, with groups having lower risks of stroke associated with smaller differential QALYs.

There is no subgroup in which the probability of apixaban being the most effective is below 50%, and none where the probability of warfarin being the most effective is above 5%. The sensitivity analyses indicate that the parameters to which the outcome was most sensitive were stroke rates and vascular death rates.

We are aware of two other adjusted,[27,28] and one unadjusted[29] indirect treatment comparisons. Lip et al.[28] concluded that there were no discernable differences among

treatments, while the analysis by Mantha et al,[27] despite being based on the same clinical trial data, indicated that apixaban was equally effective to dabigatran 150mg, more effective than rivaroxaban, and associated with less major bleeding than both. The crude estimates of net clinical benefit calculated by Banerjee et al.[29] for a Danish population are subject to bias, as the odds ratios derived from the trials were not adjusted. None of the analyses modelled patients representative of the US atrial fibrillation population, used a preference-based, patient-centred outcome measure, used an appropriate time horizon of analysis or considered alternative scenarios of analysis.

Our analysis, by contrast, adopts a lifetime horizon, uses QALYs to synthesise the differential impacts of benefits and harms on health, and considers both structural and parameter uncertainty. QALYs may reveal differences among treatments which might be less apparent when considering individual clinical events. Adjusted, indirect treatment comparisons are accepted by healthcare decision-makers across several jurisdictions as the method of choice in situations where data from head-to-head trials are unavailable[30]. This Bayesian approach results in a meaningful outcome for prescribers, that is, the probability of a treatment being the best option. Judgements based on confidence intervals and hypothesis tests, based on the frequentist notion of assuming the null hypothesis until sufficient evidence indicates otherwise, can be criticised as inappropriate in this context, as decisions regarding treatment alternatives cannot be deferred as such evidence is unlikely to become available. Moreover, a lack of statistical significance does not necessarily imply equivalence in outcome[31].

There are potential caveats to our CER methodology, however. First, there are many important differences across trials in terms of their design (e.g. RE-LY being open-label and the use of sham INR testing only in ROCKET-AF), patient populations (e.g. higher risk of stroke, greater experience of previous stroke or TIA, and less time in INR range in ROCKET-AF) and reporting (e.g. difference in the definitions of some clinical events). These have been discussed extensively elsewhere[14,28,32] and, collectively, potentially undermine the assumption necessary for indirect comparison methodology, that any such differences do not affect the comparative effectiveness of the treatments being assessed. Although there is no method of testing the validity of this assumption, there is no prospect of a head-to-head comparison among newer anticoagulants and prescribers will in any case make qualitative judgements or naïve, unadjusted comparisons of competing treatment options. Our analysis is a more valid approach than simply comparing individual trials or trial arms in an unadjusted way[33].

Second, the modelled extrapolation to a lifetime horizon of analysis is necessary to reflect differential impacts of treatments on health and survival that extend beyond the protocol-defined trial follow-up period[34]. The analysis used a discrete event simulation method, given there are no obvious discrete disease states into which patients can be classified[11]. However, this required an assumption that risk equations derived from 2-year data apply beyond that time. Relaxing this assumption by analysis at 2-years resulted in the same rank ordering of net health benefits, as did the use of an alternative, Markov model structure.

Despite these limitations there was a high level of consistency in the ranking of treatment effectiveness across all the different simulations performed. Had the results been dependent on any specific modelling assumption, then this would be apparent in the sensitivity analysis. We can reasonably conclude that any biases in our analysis, if any are present, are inherent in the data and therefore impossible to correct under any modelling framework.

It is important to note that the analysis did not consider additional factors that impinge on treatment choice. These include cost-effectiveness[10], patient convenience, preference (or

aversion) to individual treatments[35], the relative forgiveness of treatments to missed doses[36], the lack of antidotes to over-anticoagulation with the newer oral anticoagulants[37], the merits or otherwise of patients being monitored regularly when prescribed warfarin, and longer term and rarer adverse events that might only become apparent with more extensive experience of use in routine practice[38,39,40]. Furthermore, the newer agents also interact with other drugs and there are specific safety considerations in certain vulnerable populations (e.g. the very elderly and those with severe renal impairment). There may also be sub-group(s) of patients, which were not explored in the present analysis – such as those with genetic polymorphisms of *CYP2C9* or *VKORC1* – in which the balance of harms and benefits differ significantly from the mean[41].

There is no doubt of the efficacy of the newer oral anticoagulants and the favourable risk-benefit profile when compared to warfarin in the pivotal trials; however there are important differences among the agents and our analysis currently points to the likely superiority of apixaban over others. We recommend, however, that analyses of population databases of real-life user populations are performed to test hypotheses derived from our model. Certainly our results, and those from any observational studies, would not be expected to supplant evidence from randomised controlled trials, but should to be kept under review as the evidence matures.

Methods

Comparative effectiveness was assessed using an indirect analysis that extrapolated benefits and harms to a lifetime horizon, consistent with AF being a lifelong condition requiring indefinite treatment.

The analysis is based on a discrete event simulation model which we have described previously[10], and which allows for explicit incorporation of both structural and parameter uncertainty[11]. The model simulates the clinical events and outcomes experienced by individual patients. The risks of their occurrence are determined from patients' characteristics which are updated according to time and event history. Comparative effectiveness was determined from incremental net health benefits, measured as the differences between treatments in QALYs, and from modelled clinical event rates[10,12].

Model population

In the base-case analysis, patients' baseline characteristics, which were assumed to be uncorrelated, were representative of the stroke risk profile of the US atrial fibrillation population[13]. Patients had a mean age of 73.0 years, with 38.8%, 36.8%, 18.0%, 6.4% having $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack) scores of 1, 2, 3 and ≥4 respectively[13].

For each treatment, identical cohorts of 100,000 patients were generated. Each patient was given a simulated set of characteristics consisting of the presence or absence (at the start of the simulation) of the following: hypertension, diabetes mellitus, congestive heart failure, prior stroke, prior transient ischemic attack, prior myocardial infarction and prior intracranial hemorrhage, drawn from binomial distributions based on the probability of having each condition at baseline (table 3).

Interventions

The analysis considered a dose of 5mg twice daily of apixaban, and the licensed doses of dabigatran 150mg twice daily, rivaroxaban 20mg once daily, and dose-adjusted warfarin.

Clinical parameters

Annualised clinical event rates were extracted from the RE-LY, ROCKET-AF and ARISTOTLE trials[7,8,9] identified from a systematic review of the literature[14]. Based on the method of Bucher et al,[15] indirect comparisons were adjusted according to the results of their direct comparisons with warfarin. This adjustment accounts for differing baseline risks between trials by assuming a constant relative treatment effect e.g. for two trials comparing A and B, and B and C, with relative risks for a given event of RR_{AB} and RR_{BC} respectively, the indirect, relative effect of C versus A is estimated as:

$$\ln(RR_{AC}) = \ln(RR_{AB}) + \ln(RR_{BC})$$

Event rates for dabigatran, apixaban and rivaroxaban were calculated by multiplying relative treatment effects by warfarin event data, calculated from a meta-analysis of the warfarin arms of the three trials (table 4). Hypertension and diabetes incidence rates were taken from US general population data[16,17], as were age-specific non-vascular mortality data[18], all with the assumption these accurately reflect the atrial fibrillation population.

Whenever the necessary data were not available (e.g. a particular parameter was not reported for a given trial), values were imputed, based on data from the other trials and US population data (tables 4,5). All assumptions were assessed through sensitivity analysis (see structural sensitivity analysis, below).

In order to better reflect the use of oral anticoagulants in routine care, the analysis also includes the trial-derived probabilities of (and reasons for) discontinuation of treatment. Patients who discontinued dabigatran, rivaroxaban or apixaban because of a bleed or who discontinued warfarin for any reason were assumed to be switched to aspirin, whilst other discontinuing patients were switched to warfarin. This assumption was tested in a sensitivity analysis. Relative risks of events for aspirin came from a published meta-analysis of trials comparing warfarin and aspirin[19], and the AVERROES trial comparing apixaban with aspirin in patients deemed unsuitable for vitamin K antagonist therapy[20].

QALYs were discounted at 3% per annum to reflect time preference[21], but no discounting was applied to discrete clinical events.

Utility estimates

The age-adjusted baseline health utility for a person with atrial fibrillation, together with the utility decrements associated with cardiovascular sequelae (excluding stroke) and hemorrhagic events, were taken from the EQ-5D scores in a US Medical Expenditure Panel Survey of several thousand patients[22,23]. The permanent utility decrement associated with stroke was derived from the European Stroke Prevention Study, based on the proportions of disabling to non-disabling strokes (43% of non-fatal strokes were non-disabling across RE-LY, ROCKET-AF and ARISTOTLE). The analysis incorporated utility losses inherent to warfarin (e.g. as a result of monitoring), and aspirin (assumed to be the same for dabigatran, rivaroxaban and apixaban)[24]. Multiple utility decrements were assumed to be additive and utility values are given in table 5.

In order to assess the sensitivity of the model to the choice of utility parameters, a sensitivity analysis was conducted, replacing base-case utility values with those from an alternative cost-effectiveness study in atrial fibrillation[25].

Parameter sensitivity analysis

Univariate sensitivity analyses of each parameter in the model were conducted to assess the effect of varying assumptions on the stability of the results. 95% confidence intervals were used as the upper and lower limits for parameters or, where these were not available, plausible percentage ranges.

A probabilistic parameter sensitivity analysis was also conducted as a Monte Carlo simulation of 2,000 sets of parameters sampled from appropriate distributions. This provided estimates of the 95% central ranges (2.5th to 97.5th percentile) for clinical event rates and net health benefits, and the probability of each treatment option resulting in the highest net health benefit.

Structural sensitivity analysis

The model necessitated a large number of assumptions, either for simplification purposes or because the desired data were not available in the necessary format. The robustness of the results in relation to different assumptions was assessed quantitatively.

Univariate analyses considered the different options presented in etable 1. A probabilistic analysis was performed by sampling 10,000 times, at random, from the subspace of possible structural assumptions, with each assumption being equally likely to be selected. As previously, the outputs are presented as the probabilities with which each treatment option results in the highest net health benefit.

In order to assess whether the choice of a discrete event simulation framework had a significant impact on the results, a secondary analysis was performed, replacing our simulation model with a published Markov model[26].

Scenario analyses

Subgroup analyses were performed to calculate the net health benefits (and associated 95% central ranges) in the following pre-specified populations. Analyses for patients aged 75 or older; patients with a $CHADS_2$ score of 3 or more; patients with the baseline characteristics of those in each of the three studies; and patients who have previously had a stroke or transient ischemic attack were performed by altering the baseline patient characteristics in the model. Separate, indirect comparisons were made for patients with impaired renal function (30-50mL/min creatinine clearance); and patients who were naïve to vitamin K antagonist treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

What is the current knowledge on the topic?

Dabigatran, rivaroxaban and apixaban are effective alternatives to warfarin for the prevention of thromboembolic stroke in patients with atrial fibrillation. However there is no evidence on their direct comparative effectiveness.

What question did this study address?

The study addressed the question of which oral anticoagulant is most effective, in terms of modelled quality-adjusted life-years. An indirect treatment comparison was made in patients who are representative of the US atrial fibrillation population.

What this study adds to our knowledge

Compared with the alternatives, apixaban was ranked highest both in terms of the absolute number of QALYs accrued over a lifetime, and the probability of achieving the greatest QALY gains.

How this might change clinical pharmacology and therapeutics

This evidence can help inform treatment selection, particularly as there is no prospect of a definitive trial to compare each treatment directly.

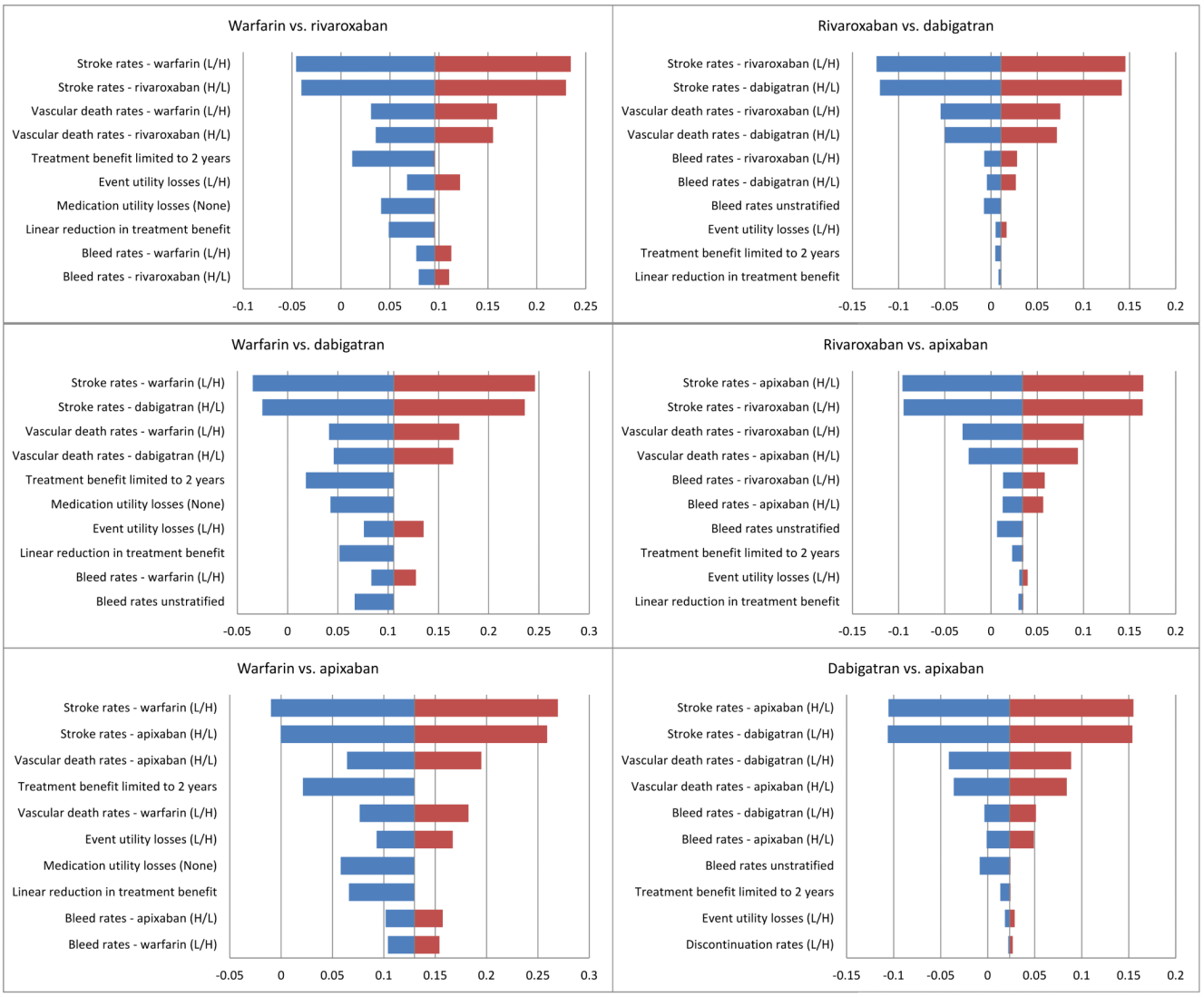

Figure 1.
Each figure presents the ten parameters which led to the greatest change in overall QALYs. L/H refer to lower and higher limits of parameter estimates.

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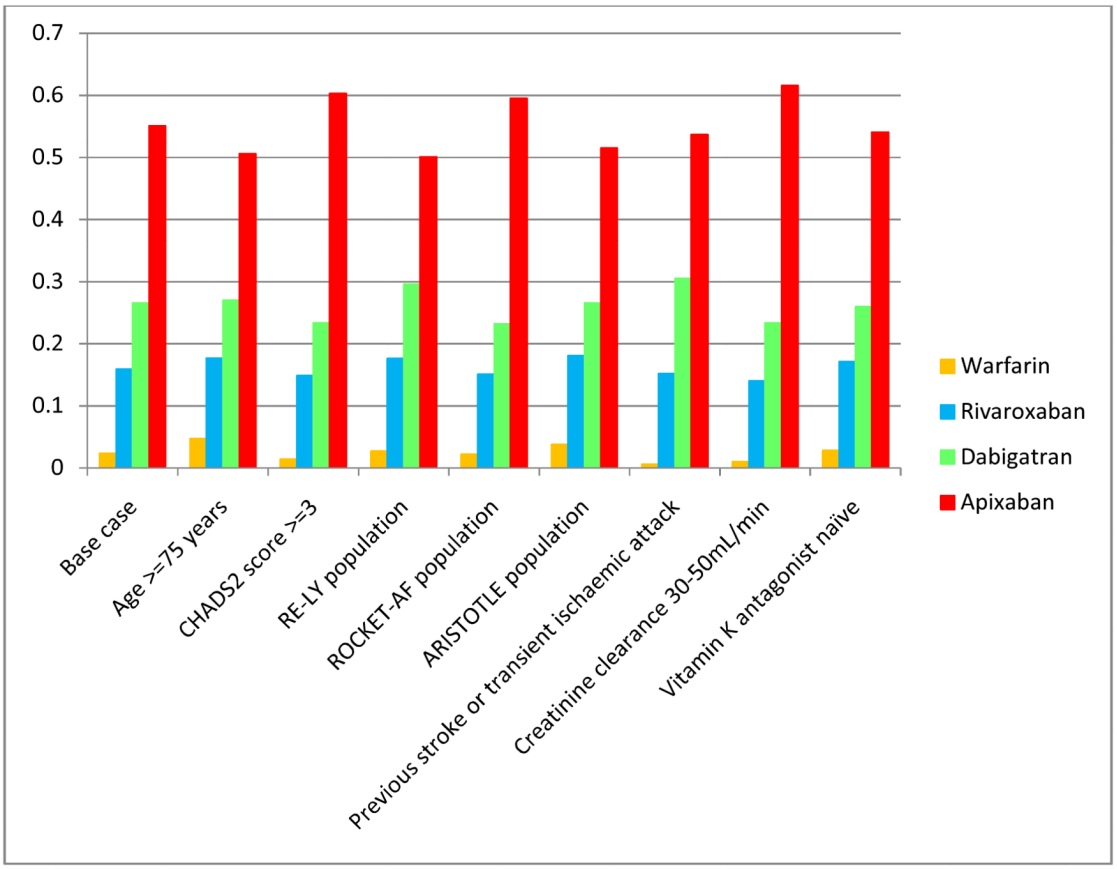

Figure 2.
Probability of each treatment is the most effective, based on accrual of most lifetime QALYs, for each identified patient subgroup.

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Table 1

Lifetime estimates of event rates, net health benefits, and incremental differences versus comparator, derived from probabilistic sensitivity analysis

Referent	Mean estimate (95% central range)	Mean difference (95% central range)	Comparator
Quality-adjusted life-years (QALYs)			
Warfarin	5.636 (5.546, 5.733)	−0.095 (−0.242, 0.052)	Rivaroxaban
Rivaroxaban	5.731 (5.631, 5.834)	−0.011 (−0.164, 0.144)	Dabigatran
Dabigatran	5.742 (5.652, 5.854)	−0.024 (−0.174, 0.130)	Apixaban
Apixaban	5.766 (5.652, 5.881)	0.130 (−0.029, 0.265)	Warfarin
Life years			
Warfarin	9.638 (9.498, 9.737)	−0.092 (−0.286, 0.120)	Rivaroxaban
Rivaroxaban	9.729 (9.579, 9.865)	−0.034 (−0.241, 0.172)	Dabigatran
Dabigatran	9.763 (9.604, 9.893)	−0.045 (−0.254, 0.147)	Apixaban
Apixaban	9.808 (9.655, 9.946)	0.171 (−0.031, 0.362)	Warfarin
Stroke or systemic embolism			
Warfarin	0.303 (0.264, 0.339)	0.020 (−0.033, 0.074)	Rivaroxaban
Rivaroxaban	0.283 (0.238, 0.319)	0.031 (−0.029, 0.083)	Dabigatran
Dabigatran	0.251 (0.213, 0.301)	0.050 (−0.001, 0.099)	Apixaban
Apixaban	0.201 (0.169, 0.254)	−0.102 (−0.154, −0.050)	Warfarin
Transient ischemic attack			
Warfarin	0.123 (0.091, 0.158)	0.031 (−0.019, 0.084)	Rivaroxaban
Rivaroxaban	0.092 (0.070, 0.123)	−0.006 (−0.057, 0.046)	Dabigatran
Dabigatran	0.097 (0.069, 0.128)	0.020 (−0.034, 0.069)	Apixaban
Apixaban	0.077 (0.055, 0.104)	−0.046 (−0.093, 0.008)	Warfarin
Intracranial hemorrhage			
Warfarin	0.073 (0.064, 0.081)	0.014 (−0.002, 0.026)	Rivaroxaban
Rivaroxaban	0.059 (0.052, 0.066)	0.018 (0.000, 0.025)	Dabigatran
Dabigatran	0.040 (0.035, 0.047)	−0.002 (−0.015, 0.014)	Apixaban
Apixaban	0.042 (0.033, 0.047)	−0.031 (−0.046, −0.013)	Warfarin
Major bleed (including intracranial hemorrhage)			
Warfarin	0.307 (0.262, 0.347)	−0.021 (−0.076, 0.036)	Rivaroxaban
Rivaroxaban	0.328 (0.283, 0.374)	0.017 (−0.037, 0.069)	Dabigatran
Dabigatran	0.311 (0.274, 0.363)	0.069 (0.014, 0.115)	Apixaban
Apixaban	0.242 (0.205, 0.278)	−0.065 (−0.116, −0.010)	Warfarin
Non-fatal myocardial infarction			
Warfarin	0.067 (0.047, 0.086)	0.007 (−0.013, 0.029)	Rivaroxaban
Rivaroxaban	0.059 (0.043, 0.080)	−0.022 (−0.043, −0.002)	Dabigatran
Dabigatran	0.081 (0.063, 0.099)	0.019 (−0.002, 0.033)	Apixaban
Apixaban	0.062 (0.044, 0.086)	−0.004 (−0.022, 0.019)	Warfarin

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Table 2

Net benefit results for subgroups, based on probabilistic sensitivity analysis

	QALYs (Probability most effective)			
Subgroup	**Warfarin**	**Rivaroxaban**	**Dabigatran**	**Apixaban**
Base case	5.637 (0.024)	5.735 (0.159)	5.745 (0.266)	5.767 (0.551)
Age ≥75 years	3.848 (0.047)	3.940 (0.177)	3.948 (0.270)	3.972 (0.506)
$CHADS_2$ score ≥3	5.482 (0.014)	5.590 (0.149)	5.617 (0.234)	5.649 (0.603)
RE-LY population	5.658 (0.027)	5.746 (0.176)	5.769 (0.296)	5.784 (0.501)
ROCKET-AF population	5.582 (0.022)	5.666 (0.151)	5.678 (0.232)	5.710 (0.595)
ARISTOTLE population	5.651 (0.038)	5.747 (0.181)	5.761 (0.266)	5.786 (0.515)
Previous stroke or transient ischemic attack	5.460 (0.006)	5.545 (0.152)	5.562 (0.305)	5.582 (0.537)
Creatinine clearance 30-50mL/min	5.561 (0.010)	5.664 (0.140)	5.677 (0.234)	5.701 (0.616)
Vitamin K antagonist naïve	5.641 (0.028)	5.729 (0.171)	5.742 (0.260)	5.766 (0.541)

Table 3

Patients' baseline characteristics

Baseline characteristics*	RE-LY	ROCKET-AF	ARISTOTLE
Number of patients	18113	14264	18201
Hypertension[7,8,9]	78.9%	90.5%	87.4%
Diabetes[7,8,9]	23.3%	39.9%	25.0%
Heart failure[7,8,9]	32.0%	62.5%	35.4%
Prior stroke[7]	12.5%	34.4%†	11.9%†
Prior transient ischemic attack[7]	9.2%	25.3%†	8.7%†
Prior myocardial infarction[7,8,9]	16.6%	17.3%	14.2%
Prior intracranial haemorrhage[7]	3.9%	10.7%†	3.7%†

*Percentage in initial population.

†These values were imputed from the data available in the RE-LY study and the distribution of $CHADS_2$ scores at the start of the trial, which was known for all three studies, under the assumption that the ratio of strokes to transient ischemic attacks and intracranial haemorrhages would be consistent between trials. Probability of prior stroke or TIA in ROCKET-AF was 55%, and in ARISTOTLE was 19%.

Table 4

Clinical event rates

Parameter	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Aspirin
Stroke ($CHADS_2$ score ≤ 1) *	0.092	0.054	0.075†	0.068	0.149
Stroke ($CHADS_2$ score 2) *	0.141	0.082	0.126	0.121	0.227
Stroke ($CHADS_2$ score 3) *	0.196	0.116†	0.134	0.113†	0.316
Stroke ($CHADS_2$ score 4) *	0.312	0.215†	0.244	0.210†	0.503
Stroke ($CHADS_2$ score 5) *	0.290	0.240†	0.279	0.233†	0.468
Stroke ($CHADS_2$ score 6) *	0.364	0.310†	0.351	0.302†	0.587
Systemic embolism *	0.014	0.011	0.003	0.012	0.022
Pulmonary embolism *	0.008	0.011	0.009‡	0.006‡	0.013
Transient ischemic attack *	0.084	0.072	0.066‡	0.062‡	0.135
Myocardial infarction *	0.076	0.101	0.062	0.067	0.076
Congestive heart failure *	0.062	0.048	0.049‡	0.045‡	0.062
Vascular death (excluding stroke and systemic and pulmonary embolism) *	0.228	0.208	0.216	0.212	0.228
Probability of death from stroke or systemic embolism	2.546	2.546	2.546	2.546	2.546
Probability of death from pulmonary embolism	1.591	1.591	1.591	1.591	1.591
Major bleed ($CHADS_2$ score ≤ 1) *	0.261	0.198	0.225†	0.159	0.115
Major bleed ($CHADS_2$ score 2) *	0.318	0.292	0.338†	0.243	0.140
Major bleed ($CHADS_2$ score ≥ 3) *	0.443	0.467	0.480†	0.306	0.194
Probability that major bleed is intracranial hemorrhage	2.336	1.023	1.495	1.407	2.336
Minor bleed *	1.656	1.502	1.714	1.178	0.726
Diabetes *	0.141	0.141	0.141	0.141	0.141
Hypertension *	0.323	0.323	0.323	0.323	0.323
Probability of discontinuation (year 1) *	1.447	2.205	1.448	1.423	N/A
Probability of discontinuation (year 2 onwards) *	0.676	0.670	0.722	0.498	N/A

* Presented as rates per 1000 person years.

† Where stratified event rates were not available, unknown stratified risks were imputed based on the assumption that the relative risks of events for patients with different $CHADS_2$ scores would be independent of treatment.

‡ Imputed, based on the relative risks of different events from the RE-LY study, on the assumption that the relative risks of different thromboembolic events would be independent of treatment.

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Table 5

Health state utilities assigned to treatments and clinical events, and the corresponding duration of acute events.

Parameter	Value	Probabilistic sensitivity analysis distribution
Atrial fibrillation (age 67)[22]	0.774	1-Gamma (43.06,0.005)
Stroke/systemic embolism (permanent disutility)[24]	0.235	Normal (0.235,0.003)
Stroke/systemic embolism (temporary disutility)[22,23]	0.139	Normal (0.139,0.01)
Stroke/systemic embolism (temporary disutility, years)[23]	0.083	Uniform (0,0.183)
Myocardial infarction (permanent disutility)[22]	0.041	Normal (0.041,0.002)
Myocardial infarction (temporary disutility)[22,23]	0.125	Normal (0.125,0.01)
Myocardial infarction (temporary duration, years)[23]	0.083	Uniform (0,0.183)
Intracranial hemorrhage (permanent disutility)[22]	0.052	Normal (0.052,0.001)
Pulmonary embolism (temporary disutility)[22,23]	0.139	Normal (0.139,0.01)
Pulmonary embolism (temporary duration, years)[23]	0.083	Uniform (0,0.183)
Transient ischemic attack (temporary disutility)[22,23]	0.103	Normal (0.103,0.01)
Transient ischemic attack (temporary duration, years)[23]	0.014	Uniform (0,0.027)
Major bleed (temporary disutility)[22,23]	0.139	Normal (0.139,0.01)
Major bleed (temporary duration, years)[23]	0.083	Uniform (0,0.183)
Minor bleed (temporary disutility)[23]	0.060	Normal (0.06,0.01)
Minor bleed (temporary duration, years)[23]	0.014	Uniform (0.0.027)
Warfarin disutility[24]	0.013	Gamma (1.3,0.01)
Dabigatran/rivaroxaban/apixaban disutility	0.002	Gamma (0.2,0.01)
Aspirin disutility[24]	0.002	Gamma (0.2,0.01)